

## CLAIMS

What is claimed is:

1. A method for altering angiogenesis in a mammal, comprising administering to the mammal, in a therapeutically effective quantity, a drug which alters binding or interaction of an artery-specific cell surface molecule with a vein-specific cell surface molecule.
2. The method of Claim 1 wherein the artery-specific cell surface molecule is an artery-specific ligand or receptor and the vein-specific cell surface molecule is a vein-specific receptor or ligand.
- 10 3. The method of Claim 1 wherein the artery-specific cell surface molecule is an Ephrin family ligand and the vein-specific cell surface molecule is an Eph family receptor.
- 15 4. The method of Claim 3 wherein angiogenesis is inhibited and the drug interferes with binding or interaction of the artery-specific Ephrin family ligand with the vein-specific Eph family receptor.
5. The method of Claim 3 wherein angiogenesis is enhanced and the drug enhances binding or interaction of the artery-specific Ephrin family ligand with its vein-specific Eph family receptor.
- 20 6. The method of Claim 3 wherein the drug is an antagonist of the artery-specific Ephrin family ligand or an antagonist of the vein-specific Eph family receptor.

7. The method of Claim 3 wherein the artery-specific Ephrin family ligand is EphrinB2 and the vein-specific Eph family receptor is EphB4.
8. A method for selectively delivering a drug to arteries in a mammal, comprising administering to the mammal a complex comprising:
  - 5 (a) the drug and
  - (b) a component which binds an artery-specific cell surface molecule, under conditions appropriate for the component of (b) to bind the artery-specific cell surface molecule, whereby the drug is delivered to arteries.
9. The method of Claim 8, wherein the artery-specific cell surface molecule is a ligand or receptor.
10. The method of Claim 8, wherein the artery-specific cell surface molecule is an Ephrin family ligand.
11. The method of Claim 10 wherein the drug is an anti-angiogenic drug and the component of (b) is an antibody specific for the artery-specific Ephrin family ligand, or a receptor of the artery-specific Ephrin family ligand.
12. The method of Claim 10 wherein the artery-specific Ephrin family ligand is EphrinB2.
13. The method of Claim 12 wherein the drug is an anti-angiogenic drug.
14. The method of Claim 12 wherein the drug is an angiogenic drug.
- 20 15. The method of Claim 12 wherein the drug inhibits formation of atherosclerotic plaques.

16. A method for selectively delivering a drug to veins in a mammal, comprising  
administering to the mammal a complex comprising:  
(a) the drug, and  
(b) a component which binds a vein-specific cell surface molecule,  
5 under conditions appropriate for the component of (b) to bind the vein-specific  
cell surface molecule, whereby the drug is delivered to veins.

17. The method of Claim 16 wherein the vein-specific cell surface molecule is a  
receptor or ligand.

18. The method of Claim 16, wherein the vein-specific cell surface molecule is a  
10 vein-specific Eph family receptor.

19. The method of Claim 18 wherein the drug is an anti-angiogenic drug and the  
component of (b) is an antibody specific for the vein-specific Eph family  
receptor, or a ligand of the vein-specific Eph family receptor.

20. The method of Claim 18 wherein the vein-specific Eph family receptor is  
15 EphB4.

21. The method of Claim 20 wherein the drug is an anti-angiogenic drug.

22. The method of Claim 20 wherein the drug is an angiogenic drug.

23. A transgenic mouse having an indicator gene which is detectably expressed in  
cells of arteries but not cells of veins.

20 24. The mouse of Claim 23 wherein the indicator gene is inserted in an artery-  
specific Ephrin family ligand gene.

25. A transgenic mouse of genotype *EphrinB2*<sup>+/−</sup>.

26. A transgenic mouse in which *EphrinB2* genes comprise an insertion that marks all arteries but not veins.

27. A transgenic mouse of genotype *EphrinB2*<sup>taulacZ/+</sup>.

5 28. A method for identifying artery cells in a mouse having an indicator gene inserted in one or more alleles of *EphrinB2*, comprising staining a section of the mouse with a substance appropriate for detection of expression of the indicator gene.

10 29. A transgenic mouse having an indicator gene which is expressed in venous endothelial cells but not in arterial endothelial cells.

30. The mouse of Claim 29 wherein the indicator gene is inserted in a vein-specific Eph family receptor gene.

31. The transgenic mouse of Claim 30 wherein the vein-specific Eph family receptor gene encodes EphB4.

15 32. A transgenic mouse of genotype *EphB4*<sup>+/−</sup>.

33. A method for identifying vein cells in a mouse having an indicator gene inserted in one or more alleles of *EphB4*, comprising staining a section of the mouse with a substance appropriate for detection of expression of the indicator gene.

34. A method for testing an effect of a drug on growth of arteries, comprising administering the drug to a mouse having an indicator gene inserted in a gene

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specifically expressed in arteries, observing the effect of the drug, and comparing the effect to that produced in a suitable control mouse.

35. A method for testing an effect of a drug on growth of veins, comprising administering the drug to a mouse having an indicator gene inserted in a gene specifically expressed in veins, observing the effect of the drug, and comparing the effect to that produced in a suitable control mouse.

5 36. A method for identifying an arterial cell in a tissue sample from a mammal, comprising contacting the tissue sample with a molecule which binds to EphrinB2, wherein said molecule is linked to a label, and detecting the label, wherein if label is detected on a cell, the cell is an arterial cell.

10 37. The method of Claim 36, wherein said molecule is an antibody.

38. A method for identifying venous endothelial cells in a tissue sample, comprising contacting the tissue sample with a molecule which binds to EphB4, wherein said molecule is linked to a label, and detecting the label, wherein if label is 15 detected on a cell, the cell is a venous endothelial cell.

39. The method of Claim 38, wherein said molecule is an antibody.

40. A method for directing a substance to arteries in a mammal, comprising administering to the mammal a complex which comprises the substance linked to a moiety which binds EphrinB2.

20 41. A method for directing a substance to veins in a mammal, comprising administering to the mammal a complex which comprises the substance linked to a moiety which binds EphB4.

42. A method for altering development of blood vessels in a mammal, comprising administering to the mammal a soluble polypeptide comprising the extracellular domain of an artery-specific cell surface protein or a soluble polypeptide comprising the extracellular domain of a vein-specific cell surface protein.

5 43. The method of Claim 42 wherein the artery-specific cell surface protein is an Ephrin family ligand and the vein-specific cell surface protein is an Eph family receptor.

44. The method of Claim 43 wherein the Ephrin family ligand is EphrinB2 and the Eph family receptor is EphB4.

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10 45. A method for identifying a drug that inhibits interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, comprising:

15 (a) combining:

- (1) the arterial cell-specific surface molecule;
- (2) the venous cell-specific surface molecule; and
- (3) a drug to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);

20 (b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and

(c) comparing the extent determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the drug to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

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wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is less in the presence of the drug than in the absence of the drug, the drug is one which inhibits interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

5 46. The method of Claim 45 wherein the arterial cell-specific surface molecule is an Ephrin family ligand and the venous cell-specific surface molecule is an Eph family receptor.

47. The method of Claim 46 wherein the Ephrin family ligand is EphrinB2 and the Eph family receptor is EphB4.

10 48. A method for identifying a drug that enhances interaction of an arterial cell-specific surface molecule with a venous cell-specific surface molecule, comprising:  
(a) combining:  
(1) the arterial cell-specific surface molecule;  
(2) the venous cell-specific surface molecule; and  
(3) a drug to be assessed for its ability to inhibit interaction between the molecule of (1) and the molecule of (2), under conditions appropriate for interaction between the molecule of (1) and the molecule of (2);  
20 (b) determining the extent to which the molecule of (1) and the molecule of (2) interact; and  
(c) comparing the extent determined in (b) with the extent to which interaction of the molecule of (1) and the molecule of (2) occurs in the absence of the drug to be assessed and under the same conditions appropriate for interaction of the molecule of (1) with the molecule of (2);

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wherein if the extent to which interaction of the molecule of (1) and the molecule of (2) is greater in the presence of the drug than in the absence of the drug, the drug is one which enhances interaction of the arterial cell-specific molecule of (1) with the venous cell-specific molecule of (2).

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5 49. The method of Claim 48 wherein the arterial cell-specific surface molecule is an Ephrin family ligand and the venous cell-specific surface molecule is an Eph family receptor.

50. The method of Claim 49 wherein the Ephrin family ligand is EphrinB2 and the Eph family receptor is EphB4.

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10 51. A method for isolating arterial endothelial cells, comprising dissociating cells of a tissue sample comprising arterial endothelial cells, contacting the dissociated cells with a substance which binds to a cell-surface protein expressed specifically on arterial endothelial cells, and separating the cells which have bound the substance from cells which have not bound the substance.

15 52. A method for isolating arterial endothelial cells, comprising dissociating cells of a tissue sample comprising arterial endothelial cells, contacting the cells with a substance which binds to a cell-surface protein expressed specifically on arterial endothelial cells, wherein said substance is bound to a solid support, removing cells which do not bind to the substance, and releasing the arterial endothelial cells from the solid support.

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53. A method for isolating venous endothelial cells, comprising dissociating cells of a tissue sample comprising venous endothelial cells, contacting the dissociated cells with a substance which binds to a cell-surface protein expressed

specifically on venous endothelial cells, and separating the cells which have bound the substance from cells which have not bound the substance.

54. A method for isolating venous endothelial cells, comprising dissociating cells of a tissue sample comprising venous endothelial cells, contacting the cells of the tissue sample with a substance which binds to a cell-surface protein expressed specifically on venous endothelial cells, wherein said substance is bound to a solid support, removing cells which do not bind to the substance, and releasing the venous endothelial cells from the solid support.

55. Isolated arterial endothelial cells.

10 56. Isolated venous endothelial cells.

57. A method for assessing an effect of one or more drugs on arteries, comprising adding one or more drugs to isolated arterial cells, and observing the cells for the effect.

58. The method of Claim 57 wherein the cells are endothelial cells.

15 59. A method for assessing an effect of one or more drugs on veins, comprising adding one or more drugs to isolated venous endothelial cells, and observing the cells for the effect.

60. A cell line derived from arterial endothelial cells.

61. A cell line derived from venous endothelial cells.

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62. A cell line which produces a protein that is detectably produced in arteries, but is not detectably produced in veins.

63. A cell line which produces a protein that is detectably produced in veins, but is not detectably produced in arteries.

5 64. A cDNA library produced from isolated arterial endothelial cells.

65. A cDNA library produced from isolated venous endothelial cells.

10 66. A method for identifying a gene which shows differential expression in venous endothelial cells compared to arterial endothelial cells, comprising producing a transgenic mouse having an indicator insertion gene in a gene to be tested for differential expression, and observing expression of the indicator insertion gene, wherein a difference in expression of the indicator insertion gene in venous endothelial cells and arterial endothelial cells indicates a gene which shows differential expression.

15 67. A method for modifying arteries in a mammal, comprising genetically altering isolated arterial endothelial cells and introducing the altered cells into the mammal.

68. A method for modifying veins in a mammal, comprising genetically altering isolated vein endothelial cells and introducing the altered cells into the mammal.

20 69. A method for altering angiogenesis in a tumor of a mammal, comprising administering to the mammal, in a therapeutically effective quantity, a drug which alters binding or interaction of an artery-specific cell surface molecule with a vein-specific cell surface molecule.

70. The method of Claim 69 wherein angiogenesis is inhibited and the drug interferes with binding or interaction of the artery-specific cell surface molecule with the vein-specific cell surface molecule.

5 71. The method of Claim 70 wherein the artery-specific cell surface molecule is an Ephrin family ligand and the vein-specific cell surface molecule is an Eph family receptor.

72. The method of Claim 71 wherein the Ephrin family ligand is EphrinB2 and the Eph family receptor is EphB4.

10 73. A method for inhibiting angiogenesis in a mammal, comprising administering to the mammal an agent that binds to EphrinB2.

74. A method for identifying a clone comprising an artery-specific gene, comprising:

15 a) isolating arterial endothelial cells;

b) producing cDNA from the isolated cells;

c) producing a cDNA library from the cDNA;

d) screening the library, by DNA hybridization, with cDNA library probes produced from isolated arterial endothelial cells, and with cDNA library probes produced from isolated venous endothelial cells; and

e) identifying the clone comprising an artery-specific gene by its differential hybridization to probes produced from isolated arterial endothelial cells.

20 75. An antibody that binds to the extracellular domain of EphrinB2.

76. An antibody that binds to the extracellular domain of EphB4.

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